

Artificial Neural Networks for Decision-Making in Urologic Oncology

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Artificial neural networks (ANNs) are computational methodologies that perform multifactorial analyses, inspired by networks of biological neurons. Like neural networks, ANNs contain layers of simple points (nodes) of data that interact through carefully weighted connection lines. ANNs are “trained” and balanced by having been previously fed data, which the ANN uses as the means for adjusting its interconnections. Studies have shown that novel and highly accurate ANNs significantly enhance the ability to detect prostate cancer early (high sensitivity) while avoiding a greater number of unnecessary tissue samplings (high specificity). The use of ANNs in prostate cancer is ideal because of 1) multiple predicting factors that influence outcome; 2) the desire to offer individual consulting based on various tests; 3) the fact that prior logistic regression analysis results have had serious limitations in application; and 4) the need for an up-to-date tool that can apply easily to everyone. An ANN should be seen as an important tool that is complementary to the physician’s personal knowledge and judgment in making decisions.

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In earlier years, Socrates wrote: “One thing I know for sure is that I do not know anything for sure.” This statement has often been appreciated in the years since that time. The chaos theory also states, “Dynamic systems display inherently unpredictable behavior. The possible states of complicated systems are infinite and nonrepeating due to chance, yet restricted to a certain realm.”¹ So, medical science, whose main purpose should be the continuous seeking of knowledge, has now focused philosophically on its own inability to actually know and predict things. It has tried to establish things as data in a detailed manner and then to approach them in a holistic way.

In medical practice, nothing seems more critical than the decision-making and planning involved in treating oncologic patients. The well-established tumor, lymph node, and distant metastasis (TNM) staging system draws much of its power from its worldwide approval. The TNM classification describes the anatomic extent of cancer. It is based on the fact that the ideal treatment of disease, as well as survival, is mainly affected by the local extent of the tumor site and the probability of cancer in the regional lymph nodes.

The objectives of the TNM classification system are to aid the clinician in the planning of treatment, to give some indication of the prognosis, to assist in the evaluation of treatment results, and to facilitate the exchange

to refer to two of the main oncologic diagnostic and prognostic tools—have radically changed. There is a growing need for the possible incorporation of other variables that play a prognostic role in a patient with a malignancy, such as serum factors values or even tissue genetic varieties.

What exactly does artificial intelligence do, in a better way than we are used to, in regard to oncologic decision-making? In what way could clinicians and patients benefit from artificial neural networks (ANNs), and what makes ANNs so attractive?

ANNs are computational methodologies that perform multifactorial analyses, inspired by networks of biological neurons. Like neural networks, ANNs also contain layers of simple points (nodes) of data that

plicated data in a more successful way than simple regression analysis can, provided that it is correctly “trained” and balanced by having been previously fed data. Urology provides a good example of the need for an ANN: prostate cancer is a disease that needs more than one option for the physician to be able to determine diagnosis, staging, and treatment. In prostate cancer, many diagnostic variables have to be taken into consideration for individual staging. Will the patient then follow a path of curative, palliative, or salvage treatment?

After its enthusiastic incorporation in urology, the measurement of prostate-specific antigen (PSA) serum levels was found not to be clinically sensitive enough to make various decisions for the patient. After all, approximately 30% of men who undergo radical prostatectomy and 25% of men who are diagnosed with prostate cancer have a PSA value of less than 4 ng/mL.^{4,5} Even lowering the PSA cut-off point to perform a prostatic biopsy, in an attempt to optimize its ability to detect cancer, would create different kinds of problems. Djavan and colleagues documented that the incidence of prostatic cancer in men with a PSA value within the “gray” zone of 4.0–10.0 ng/mL is approximately 22%, while another 10% is in the repeat biopsy.⁶ Similar findings in men whose PSA value ranges from 2.5 to 4.0 ng/mL would increase the potential need for a biopsy in many men who currently are being excluded. Indeed, the majority of men undergoing a prostate biopsy will have a negative result for cancer, and the costs of these biopsies are huge.

The ever-increasing pool of men who have indications of requiring a prostatic biopsy strongly indicates that a new diagnostic tool is needed that would maintain or even increase diagnostic performance while reducing

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of information.² TNM can also play a role in assessing the management of patients and putting a limit on certain therapeutic options for certain patients. TNM practically serves as the first means of selecting patients. This is also basically the main purpose of an artificial neural network (ANN).

There are, however, some handicaps in the use of the TNM system. It appears to be rather slow in incorporating changes, and there must be worldwide agreement before a change is made. Moreover, the TNM system is based on anatomy at a time when the science of oncology is based increasingly on biology and biomolecular characteristics.³

In our time, we have been witnessing practically a flood of data in every area of our speciality. Especially in oncology, the ways of communicating in pathology or imaging—just

interact through carefully weighted connection lines. The weight-balance of these lines is accomplished by a training session of input data, to be used by the network as the means for adjusting its interconnections. Many applications of ANNs are present in our everyday life, and recently their applications in medicine have been growing rapidly. For example, ANNs have been trained and used to identify any peculiar or abnormal behavior of a variable. To use the analogy of commerce, it is as if someone has noted an unusual purchase on your credit card number and calls you just to make sure the card has not been stolen. In addition, through a combination of physics, ANNs have been used as a device to warn drivers when a car turns incorrectly, and the ANN may perhaps correct that action.

Thus, an ANN can deal with com-

the amount of unnecessary biopsies. Moreover, because there is a substantial overlapping of PSA values between men with benign prostatic hyperplasia or prostatitis and men with prostate cancer, this new diagnostic tool should also incorporate the most important of the PSA-based prostatic variables, such as free/total PSA (f/t PSA), prostate-specific antigen density (PSAD), PSA transition zone (PSA-TZ), and perhaps other clinical determinations like the digital rectal examination (DRE) or the size of the prostate. Each one of the PSA serum parameters adds a little to the PSA sensitivity, while there is a debate over whether one or more should be used so as to rule out most unnecessary biopsies.

Artificial Neural Networks (ANNs) for Early Detection of Prostate Cancer

Recently, there has been some bibliographic data about the use of ANNs in the diagnosis of prostate cancer. In a study by Babaian and colleagues,⁵ a neural network-derived algorithm was developed based on retrospective data that studied 151 men with PSA values from 2.5 to 4.0 ng/mL, who underwent an 11-core, multisite, directed biopsy. The ANN used variables such as age, total PSA, prostatic acid phosphatase (PAP), creatinine kinase, and free PSA while it consisted of three individually trained networks that were developed with data from retrospective studies coming from three institutions. Cancer was detected in 24.5% (37 of 151) of the patients. A comparison of the sensitivity, specificity, and negative and positive predictive values between the neural network algorithm and the other PSA parameters showed that the ANN index was significantly better in terms of specificity when sensitivity was constantly held at 92%. In terms of a receiver operating characteristic

(ROC)-curve analysis and area under curve, however, the ANN index did not show any better results; but as the authors comment, this discrepancy could have been caused by the difficulty in using the ROC kit to monotonically map such a complicated,

models of exclusion criteria with respect to specificity, sensitivity, and positive predictive value (PPV) or negative predictive value (NPV).

A recent trial by Finne and colleagues⁹ reported similar findings. Thus it is becoming evident that these

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computationally generated index such as the ANN index. On the other hand, ROC curve analysis failed to demonstrate any statistically important difference between the study tests. This does not mean, however, that there is no clinical significance in the better rates that were accomplished by the ANN index. The authors concluded that their ANN index outperformed all the other PSA enhancements and that there would be an important reduction in the costs of unnecessary biopsies to the health care system by an additional 39%, if their ANN-index were used instead of f/t PSA.

In another, similar study by Djavan and associates,^{7,8} two ANNs for men with a total PSA of 2.5–4.0 ng/mL as well as 4.0–10.0 ng/mL were developed. They also tested the predictive accuracy of the ANN in comparison with conventional statistical analysis of standard PSA parameters. The authors used the variables % PSA, PSA-TZ, prostate-specific antigen velocity (PSAV), free PSA (fPSA), TZ volume, total PSA (tPSA), and PSAD as the final input variables for their ANN model (with the exception of tPSA, TZ volume, PSAV, and DRE for their ANN for PSA levels from 2.5 to 4.0 ng/mL, as these variables did not contribute to the predictive ability of the network). Their conclusion was also that both ANN models were superior to the other

novel and highly accurate ANNs represent a significant enhancement to our ability to detect prostate cancer early (high sensitivity), while avoiding a greater number of unnecessary tissue samplings (high specificity).

ANNs for Prostate Rebiopsy

What, however, is the performance of ANNs in terms of predicting the outcome of repeat biopsies and determining the need for a rebiopsy in cases where the initial biopsy is negative? This is one of the most confusing questions for both the urologist and the anxious patient who has had a persistent increase in PSA and negative findings from the biopsy. The work of Remzi and associates^{10,11} tries to incorporate the use of ANNs in predicting the outcome of a rebiopsy. These authors¹⁰ input ANN variables such as age, tPSA, % free PSA ratio, PSA velocity, and the transrectal ultrasound (TRUS) variables of prostate volume, TZ-volume, PSA density, and PSA-TZ-density. The diagnosis of prostate cancer was set in 10% of the patients with a previous negative biopsy. The writers estimated that when specificity remained at 95%, then the sensitivity of the ANN as a tool for prediction was 68%, with 40% for % free PSA ratio, 34% for TZ-volume, and 30% for PSA-TZ-density. There are also promising reports on the newly emerging complex (cPSA), which can

be used successfully in ANNs for the prediction of the outcome of repeat prostate biopsies.¹²

ANNs for Prostate Cancer Staging

Trying to stage disease in patients with prostate cancer or many other malignancies by means of anatomic factors alone is anachronistic. It has been practically outdated and abandoned by today's clinicians or oncologists, especially in the treatment of prostate cancer, where technology has provided newer and far more accurate tools of staging. The accurate prediction of staging by means of substantial preoperative parameters can help in selecting the best therapeutic procedure for a patient. Which, however, of these diagnostic tools has a greater impact on staging? Moreover, based on what grounds should the urologist employ these tools in decision making for further evaluation and treatment?

Interesting data have been published recently that try to incorporate ANNs in these kinds of evaluations. Murphy and colleagues¹³ used the outperformance of the clinical sensitivity of ProstaScint in detecting soft-tissue metastases to evaluate the predictive potential of various serum tests for their relevance to the staging outcome. Although traditional statistical analysis showed little value in correlating these variables to the status of disease progression—something that was more or less expected—the finding of the ANN used in this study showed that PSA markers and a ProstaScint scan contributed in a significant manner to the designation of nodal status (N) or metastatic disease (M), something that was not proven with tumor (T) stage. Of course, this result needs to be proven in further studies and in more randomized populations than the one selected by the authors.

In a review study, Han and colleagues¹⁴ included the input variables

of preoperative clinical and pathologic parameters from patients after a radical prostatectomy in order to retrospectively feed an ANN so that it would test their predictive value in staging the disease. The neural network used in this application was a multilayer perceptron, which typically has a standard, feed-forward topology and successive layers of adaptive weights. Overall, the ANN outperformed nomograms in predicting the pathologic stage at the time of surgery and was more accurate in terms of sensitivity and specificity; it also has a larger area under the ROC curve than the logistic regression based on nomograms. It is important to note that among its authors this study included Alan Partin, who

suggest the relationship that the output of the ANN might have with the prevalence of LN-positive cases and were also able to interpret the risk of similar ANN-score patients in LN-positive status. They were thus able to calculate the individual risk of the LN-positive status in patients with risks similar to those calculated by the ANN.

ANNs in Predicting Biochemical Failure

Another issue of great controversy is the prediction of progression, ie, biochemical failure, after a radical prostatectomy and the estimate for the need for adjuvant therapy by either local irradiation, hormonal ablation, or chemotherapy. A group

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admits that ANN served better than the Partin nomograms that are currently the gold standard for predicting the staging of the disease.

In a relevant published work, Batuello and colleagues¹⁵ demonstrated the performance of a suitably trained ANN in predicting the invasion of the lymph nodes (LNs). The aim of using the ANN was to identify the characteristics of LN-positive individuals. Because only 4.6% of the cohort of patients was actually LN positive, the ANN tried to recognize the characteristics of these individuals by classifying the patients as LN-negative. In order to achieve minimal error, the training algorithm treated the scarce positive cases as "noise." By increasing the LN-positive cases empirically to 25%, the authors achieved a statistically important impact of LN-positive status in the weight-adjusted interconnections of their ANN. The authors were able to

of patients (published data reveals as many as 59%) will eventually be found with positive surgical margins after radical prostatectomy, if this operation were performed because of presumed organ-confined disease. The finding of a cancer-positive margin would suggest failure in the excision of all traces of local disease as well as the risk of biochemical and clinical progression. Serious decisions need to be made as to who would benefit the most from adjuvant therapy without taking unnecessary risks in terms of the morbidity and mortality that accompany the administration of adjuvant agents. A urologist must also consider the differences in statistical importance of several pathology variables when predicting biochemical failure. Although most patients with a pathologically confirmed status of prostate cancer (pT2a) will remain progression-free after a radical prostatectomy, there is a subset of those

patients in the “gray” zone that eventually develops progression. ANNs could play a key role in addressing these questions as well. In an article by Mattfeldt and colleagues,¹⁶ a comparison of two groups of 20 patients (with or without progression of disease) that were matched for age, preoperative PSA, and duration of follow up yielded some promising results. An ANN-predicting cancer progression was measured by only three variables—Gleason score, World Health Organization grade, and tumor diameter. Similar results were reported by Potter and associates¹⁷ in a group of patients with intermediate-risk of progression (T1b to T2c N0 M0, Gleason score 5 to 7) by using a “genetically” engineered ANN (GENN). Genetically engineered means that the ANN develops its architecture and selects the fittest solutions so that ultimately an optimal network may evolve. The authors used variables such as prostatectomy pathologic findings and age, but also DNA ploidy and the variance of 41 different nuclear descriptors. There were three models of ANN according to the variables used: 1) pathology and age; 2) nuclear morphometric descriptors and DNA ploidy; and 3) all variables included. The accuracy of the three GENN models was 74.4%, 63.1%, and 73.5% in training and 74.3%, 80.0%, and 78.1% for testing, respectively. Data were then analyzed by logistic regression and Cox proportional hazards modeling. Logistic regression analysis maximized performance in the training sets only to be outperformed by the ANNs in testing sets. In other articles^{18–20} the ability of ANNs to assess the preoperative risk of progression was similarly shown.

When and How to Use ANNs

In ANN methodology, a researcher would typically start with a compendi-

um of data from a single population of patients. These data are then divided, at random, into three subsets: training, validation, and testing. The training set is used for the adjustment of weights of interconnections during training. The testing and validation set is then used to decide when to stop training.²¹ The setting of prostate

rather than being in a text format. Because of the sensitive nature of the training regarding the input of data, ANNs tend to be somewhat of a trap for the unsuspecting clinician. As the application of this highly sophisticated methodology emerges, there are some serious considerations that scientists must deal with. First of all, the clini-

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cancer problematics is ideal for the use of an ANN because of several characteristics: 1) multiple predicting factors that influence outcome; 2) the desire to offer individual consulting based on various tests; 3) the fact that prior logistic regression analysis results have had serious limitations in application; and 4) the need for an up-to-date tool that can apply easily to everyone.

For the first time, data from unused records that many institutions have gathered over the years can play a serious role in making future decisions. The application of ANNs has already begun in the med-

cian must be thoroughly knowledgeable about the use of ANNs, their methodology, their input of data, and their limitations, because there is a reasonable fear that data fit for one population might be used to make decisions in another for which it is unfit. That fear is more evident because of the easy availability of the ANN on the Internet, which may change from a privilege into a handicap. Differences among races, time of data collection, countries, or health care systems and their screening habits, can seriously influence the outcome of an ANN. Moreover, there are serious limitations arising

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ical field in terms of imaging, instrument monitoring, drug research, and informatics. The wealth of experience gained in these fields can be used for the benefit of all newly emerging medical-decision applications.

Precautions in Using ANNs

In medicine, the key element in using ANN technology is the construction of a quality medical record that can be easily accessed and can provide specific medical data that is coded

from the variability of data due to technical differences in monitoring technology, which can be thought of as an uncontrolled variable. A database system must also ensure confidentiality, and the encoding of medical data by common shared standards is still under way. Now that the new technology is emerging, however, proper databases can be constructed and used as input data (something that is somewhat limited at present).

Future Aspects

Will the ANN replace human differential diagnosis and thinking? In the environment of construction of great bases of medical data, it will be easy to make individual patient predictions, to select diagnostic and therapeutic options, and even to perform more sophisticated functions like developing a system that will, for example, propose new patterns of disease or report treatment-responses. At that time, the autonomy of the system could render the need for a physician unnecessary, because the system will be able to perform individual counseling and plan for a patient based on a huge database of patterns in diagnosis, therapy, or follow-up. Could this be the end of traditional human communication and consultation between the physician and the patient? There will certainly be some slow approval of these changes, especially from older clinicians who, for so many years, have been used to making decisions in a certain way. We might, however, persuade clinicians in our specialty to change their ways through the clear demonstration

of the clinical benefits achieved by the incorporation of such procedures.

Conclusion

There are still some controversies surrounding the early detection of prostate cancer. If prostate cancer is suspected, then a patient is scheduled for a biopsy. In case of a negative result, the urologist should advise the patient of the need for a rebiopsy or perhaps for watchful waiting. If cancer is finally found, then the problematic questions are whether it is actually an organ-confined disease or the patient is hiding extraprostatic disease? A treatment plan must also be devised. Will the patient receive radical curative or palliative treatment? One thing for certain is that the patient would benefit from early decision planning before a decision is made.²²

For the first time, we have the power of a tool that is equally available and easily accessible to any urologist. This promising tool uses up-to-date data and demonstrates a flexibility in learning that should provide proper outcomes. The availability of these data to every patient

is a key issue to health care systems, because the construction and use of electronic medical records comes with many advantages such as easy accessibility and back-up technology.

Currently, we should consider the ANN to be an important tool for consultation that should never replace our personal knowledge and judgment. By doing so, it becomes complementary to our decision making. The ANN must be used as a unique tool to test each patient's risk assessment in order to give the patient the highest level of predictive accuracy. This important prognostic tool could produce radical changes in the way we make decisions because it provides an easy way for the patient and the doctor to understand medical facts. It could also lead to improvement in the accuracy of our diagnostic tools, and by reporting the effects of selective treatment options, it may also affect our treatment decisions. ■

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Main Points

- Artificial neural networks (ANNs) are computational methodologies that perform multifactorial analyses, inspired by networks of biological neurons. Like neural networks, ANNs contain layers of simple points (nodes) of data that interact through carefully weighted connection lines. The weight-balance of these lines is accomplished by a training session of input data, to be used by the network as the means for adjusting its interconnections.
- An ANN can deal with complicated data in a more successful way than simple regression analysis can, provided that it is correctly "trained" and balanced by having been previously fed data.
- Studies have shown that these novel and highly accurate ANNs significantly enhance the ability to detect prostate cancer early (high sensitivity), while avoiding a greater number of unnecessary tissue samplings (high specificity).
- Overall, ANNs outperformed nomograms in predicting the pathologic stage at the time of surgery and were more accurate in terms of sensitivity and specificity; an ANN also has a larger area under the receiver operating characteristics curve than the logistic regression based on nomograms.
- Prostate cancer problematics are ideal for the use of ANNs because of several characteristics: 1) multiple predicting factors that influence outcome; 2) the desire to offer individual consulting based on various tests; 3) the fact that prior logistic regression analysis results have had serious limitations in application; and 4) the need for an up-to-date tool that can apply easily to everyone.
- An ANN should be viewed as an important tool that is complementary to the physician's personal knowledge and judgment in making decisions.

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